DOCKET NO: 278157US

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
MARIE-CLAUDE GINGRAS, ET AL.	: EXAMINER: BELYAVSKYI
SERIAL NO: 10/021,509	:
FILED: DECEMBER 7, 2001	: GROUP ART UNIT: 1644
FOR: TREM-1 SPLICE VARIANT FOR USE IN MODIFYING IMMUNE RESPONSES	:

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This brief is submitted in response to the rejections dated October 21, 2005.

REAL PARTY OF INTEREST

The real party of interest herein is GenePrint Corporation, Houston, Texas.

RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any related appeals and/or interferences to the present case.

STATUS OF CLAIMS

Claims 1, 3, 5, 11, 15, 16 and 40-42 are active in this application, are rejected and appealed. It is noted that while Claim 42 was indicated as being withdrawn (October 21, 2005

Official Action) because of the dependency to another withdrawn claim (39—now cancelled), the amendment to claim 42 to depend from claims 1 or 3 changes its status to active.

STATUS OF AMENDMENTS

There are no outstanding amendments in this case as all amendments previously filed in response to the October 21, 2005 Official Action have been entered for the purpose of this Appeal (Advisory Action mailed August 24, 2006).

SUMMARY OF CLAIMED SUBJECT MATTER

The invention currently under examination is to a method of modulating an immune response comprising administering to an animal, in need thereof, a composition of soluble polypeptides with at least a portion of amino acids 1 to 136 of SEQ ID NO:2 or a polypeptide mimetic thereof, in an amount effective to modulate the levels of TREM-1 and /or TREM-1SV ligand binding activity whereby the immune response is modulated in the animal.

Claim 1 is supported on pages 4-7, pages 11,12, page 19, figures 1 and 4 of the specification as originally filed. Claim 40 is supported at paragraph [0033] in the specification. Claim 41 is supported by Example 11. Claim 42 is supported at paragraph [0031] .

As discussed in the present specification, TREM 1 is a receptor of activation in macrophages. TREM 1 includes a soluble extracellular domain and a hydrophobic transmembrane domain (see Fig. 1) that when triggered by its ligand, the ligated complex induces macrophage activation. TREM 1-SV is a variant of TREM-1 that is not anchored in the macrophage cell membrane but free to capture TREM-1 ligand. When TREM-1 ligand is captured by TREM 1-SV the TREM-1 receptor complex is not triggered and the

macrophages are not activated thus permitting the modulation (up or down activation) of macrophages, which in turn modulates the immune response.

GROUNDS TO BE REVIEWED ON APPEAL

A. The first ground of rejection to be reviewed on appeal is whether Claims 1, 3, 5, 11, 16, 40 -42 are sufficiently describe in the specification so as to be enabled under the meaning of 35 U.S.C. § 112, first paragraph.

B. The second ground of rejection to be reviewed on appeal is whether Claims 1, 3, 5, 11, 15, 16, 40 -42 are anticipated by the disclosures of U.S. patent no. 6,420,526 or U.S. patent no. 6,504,010 under the meaning of 35 U.S.C. § 102(e).

C. The third ground of rejection to be reviewed on appeal is whether Claims 1, 3, 5, 11, 15, 16, 40 and 41 constitute new matter under the meaning of 35 U.S.C. § 112, first paragraph.

ARGUMENTS

A. Claims 1, 3, 5, 11, 15, 16, and 40-42are enabled by the specification and the knowledge in the art meeting the requirements set forth in 35 U.S.C. 112, first paragraph

As alleged support for this rejection, the Office contends that the specification 1) does not teach how to effectively modulate any immune response, and 2) the compounds of this invention are not the compounds used in the art . This position appears to be based on the lack of a working example in the specification and the belief that practicing the invention would require undue experimentation. Appellants disagree.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation MPEP 2164.01; *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). As long as the Specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). As stated in MPEP 2164.04 in order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms with corresponding scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

The disclosure for making the composition consistent with the scope of Claim1 can be found on pages 4-7,11-12, 19, Figures 1 and 4 of the specification as originally filed. The

Examiner has provided no reasonable basis to question the enablement provided for the claimed invention. Based on the specification and the additional comments below, it is clear from reading the Specification that the broad scope of the invention as recited in Claim 1 is supported and enabled.

While there is no working examples in the specification, there is sufficient guidance in the specification and in the art that provide the necessary knowledge for using the claimed methods to effectively modulate an immune response. For example, one need only perform the systemic administration of a peptide composition in a dose range between 5 and 50 mg of peptides per kg of body weight as disclosed in Bouchon et al., *Nature* 410:1103, 2001, and Gibot et al., J Exp Med. 200:1419, 2004, (each previously made of record) as recited in the claims to effectively modulate an immune response. In addition, operability of the claimed methods can be predicted by analogy to the art of Bouchon et al. and Gibot et al.

The Examiner's allegation that undue experimentation would be required to practice the claimed invention based on the perception that there is dissimilarities between the compounds of this invention and those in the art is misplaced. The fact is that there is a relationship between the structure of the TREM-1 molecules that are members of the Ig superfamily and their respective biological activity. In biology, molecules are described by their respective biological activity. In the case of cellular receptors, their respective biological activity relates to their binding sites. The specificity of TREM-1 is that it is a member of the Ig superfamily of cellular receptors as demonstrated by Kelker et al. *J. Mol. Biol.* 342:1237, 2004 and Ibid. *J. Mol. Biol.* 344:1175, 2004 (of record). The members of this Ig family are characterized by having loop domains folding on each others. It has been extensively demonstrated over the last three decades that the binding activity of these Ig superfamily receptor molecules is effected by the binding sites located in these disulfide bounded loop domains (see chapter 16 p. 427-29 of Immunology by H. N. Eisen and see

Chapter 7 pp. 7.1 -7.3 of Immunology by I. M. Roitt et al—both of record). Although, the work of Kelker et al. could not identify specifically the exact sequence of the binding site in the loop domain as pointed out by the Examiner, the work of Kelker et al. has confirmed the structure and presence of these loops domains in the different TREM-1 molecules studied. Therefore, the scientific evidence points out that the binding site activity of TREM-1 is within its the loop domain as described in figures 1, 4 and 5 of the present application because of its overall structure and its appertaining to the Ig superfamily of receptors. As cited by Kelker et al. *J. Mol. Biol.* 342:1237, 2004 " TREM-1 (Figure 2(a) and (b), cyan) maintains an overall structure that is homologous to other members of the Ig family," (see page 1240) and " Comparison of the TREM-1 structure to other members of the Ig-V Type fold demonstrates a close structural relationship." (see page 1239)

It should be noted that the statement from Kelker et al cited by the Examiner is given improper weight because it is irrelevant to the whole demonstration of the articles showing a close structural relationship between the Ig-V fold and the TREM-1 structure (i.e. the characteristic presence of the loop domain inside of which the binding site is located). TREM-1sv has the exact same sequence of the extracellular domain of TREM-1 or the TREM-1/IG1 described in Bouchon et al. Moreover, Gibot et al. obtained effective immune modulation activity with a small peptide containing only a part of the sequence loop domain being the mouse equivalent peptide of amino acid 103 to 119 of the human sequence (see Figure 4). Thus, compounds having a portion (Gibot et al.), the whole portion,or more than the whole portion (Bouchon et al.) of amino acids 36-114 of SEQ ID NO:2 all have a degree of effective immune modulation activity because they contain part of or the whole binding activity site.

As to how to define the dosage, this is routine in the field and certainly cannot be the basis to allege undue experimentation. As mentioned earlier, one can perform the systemic

administration of a peptide composition in a dose range between 5 and 50 mg of peptides per kg of body weight as disclosed in Bouchon et al. and Gibot et al as recited in the claims to effectively modulate an immune response. Moreover, as the claimed methods here relate to a therapeutic method some degree of individual variation among patients is inevitable. Medical practitioners routinely prescribe a dose of a therapeutic agent to a patient, observe the response (including any side effects), and modify the dosage or identity of the therapeutic agent depending on the individual patient's response.

The Examiner alleges that the specification does not adequately support that any immune response can be treated with any soluble polypeptide comprising at least a portion of amino acids 1 to 136 (page 6 of the October 21, 2005 Official Action). The Examiner further basis this assertion because the specification does not provide *in vivo* data. Appellants respectfully submit that the Examiner is incorrect.

The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

The specification clearly asserts that the soluble polypeptides containing the binding site activity can be used to modulate an immune response (e.g., pages 4-7) which is supported by the data discussed in the Declaration of Marie-Claude Gingras, referencing the Bouchon et al publication and the Gibot et al publication noted above. It flows quite clearly from this that the soluble TREM-1 receptor Bouchon et al. utilized uses the teachings of the present invention to show that a soluble TREM- I receptor inhibits cell functions that are activated by TREM-1 (for example, reduced the activity of TREM-1/DAP12 complex, and reduced inflammation). Thus, the soluble TREM-l receptor of Bouchon et al. was acting as a competitive inhibitor, as described by the present application. Moreover, the use of at least a portion of amino acids 1-136 of SEQ ID NO:2 or a polypeptide mimetic thereof such as the

polypeptide utilized by Gibot et al. uses the teachings of the present invention to reduce the inflammation.

Appellants assert that the quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether undue experimentation is required to make and use the invention. An extended period of experimentation may not necessarily be undue if sufficient direction or guidance is provided and those in the field usually undertake such experimentation.

The methods outlined in the specification provide sufficient directions to enable the modulation of the immune response by administering a compound that decreases the activity of DAP 1 2/TREM- 1 complex, as illustrated by Bouchon et al. and Gibot et al. *In re Colianni*, 561 F.2d 220, 224, 195 U.S.P.Q. 150, 153 (CCPA 1977). Thus, the amount of experimentation is permissible because it is merely routine and the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 5F.2d 731, 737, 8 U.S.P.Q.2D 1400, 1404 in (Fed. Cir. 1988). In light of the data presented by Bouchon et al. and Gibot et al., Appellants assert that the present invention is enabled since one of skill in the art was able to practice the invention without undue experimentation.

Yet further, it appears that the Examiner is requiring human trials as the only sufficient support for what the Examiner perceives is enablement of the claims. This is an absolutely improper standard. Although it is expected that pharmaceutical inventions will necessitate further research and development, clinical testing is not required to obtain a patent. *In re Brana*, 51 F.3d 1560, 1569 (Fed. Cir. 1995). Appelants are not required to perform FDA-type testing on humans in order to obtain a patent.

In summary:

1. The mechanisms by which the polypeptide competes for the TREM-1 ligand is described throughout the specification.

2. The structure of different TREM-1 molecules across species have been studied and regardless of their transmembrane region, their ligand binding site is a common conservative region forming a loop binding domain created by a pair of disulfides bridges, one on each end of the loop. (see Kelker et al. and see chapter 16 p. 427-29 of Immunology by H. N. Eisen and see Chapter 7 pp. 7.1 -7.3 of Immunology by I. M. Roitt et al).

3. The enablement of the claimed therapeutic action of the composition having this binding ligand activity is supported by the data in Bouchon et al., and Gibot et al..

4. One can practice the claimed invention because one can predict the therapeutic efficacy of the composition with TREM-1 ligand activity as long as it contains a portion of the TREM-1SV (see amino acids 1-136 of SEQ ID NO:2) that provides a therapeutic action.

5. One skill in the art can practice this invention based on the competitive inhibition, neutralization or enhancement mechanisms described in the specifications and in the art as practiced by Bouchon et al., and Gibot et al.

6. The sequence of the ligand binding site and its application use for therapy is well disclosed in this application and combined with the common knowledge in the art, a person has all the means to practice this invention to obtain a therapeutic action.

Taken together, the specification coupled with the knowledge in the field demonstrate that the biological activity of immune modulation of all the compounds claimed.

B. Claims 1, 3, 5, 11, 15, 16, and 40-42 are not anticipated under 35 U.S.C. 102 (e) in view of US Patent 6,420,526 or US Patent 6,504,010

A basis of the rejection is the apparent similarity of the sequence SEQ ID NO: 1825 and SEQ ID NO: 2 of this application. The Office's reliance on this is fundamentally misplaced for the following reasons.

(i) The US '010 patent

U.S. '010 describes several hundred sequences, one of which is similar to TREM-1sv strictly for the purpose of treating cancer, generally and lung cancer, specifically. In other words, US '010 describes a hypothetical therapeutic method to treat lung cancer. First, the claimed method is not treating cancer but to modulate an immune response. Second, the mechanism of action is unclear and no proof or evidence of such a lung cancer therapy using SEQ ID NO 1825 is presented in US '010 because such therapeutic effect is simply non existent and is against current understanding of how SEQ ID NO 1825 can act biologically. There is a proposed targeted mechanism of T cell activation but there is no scientific logic to support it.

Also, the US '010 disclosure does not provide enough specific guidance to specifically use the peptide corresponding to the TREM ligand binding domain and use it for a treatment regimen with the intended purpose of achieving the claimed effect, explicitly or inherently. Therefore, the claims cannot be anticipated by the US '010 patent. See *Jansen v. Rexall Sundown, Inc.* 68 USPQ2d 1154 (Fed. Cir. 2003) where the court held that "in need thereof" language is not satisfied if the active ingredient is administered for a purpose other than the claimed purpose; see also *Perricone v. Medicis Pharmaceutical Corp.*, 432 F.3d 1368; 77 U.S.P.Q.2D 1321 (Fed. Cir. 2005): ""The issue is not, as the dissent and the district court imply, whether Pereira's lotion if applied to skin sunburn would inherently treat that

damage, but whether Pereira discloses the application of its composition to skin sunburn. It does not."

In view of the above, there can be no question that the Office's rejection based on US '010 is not sustainable and should be reversed.

(ii) The US '526 patent

Similarly, the rejection based on US '526 due to an alleged inherent property of SEQ ID NO 478. It is well-established law that in order for a reference to anticipate a claimed invention, the reference or references must provide an enabling disclosure sufficient to place the public in possession of the claimed invention.[1] Likewise, this analysis extends to obviousness, where a holding of obviousness cannot be sustained unless there is some known or obvious way to make the thing or to carry out the process.[2]

US Patent 6,420,526 is very vague patent. The '526 patent describes a sequence with no details in the specifications on which sequence of the molecule has a function. Functions are associated with translated proteins not with a EST DNA sequence. US Patent 6,420,526 is a multiple EST sequence patent (186 all together) containing the sequence 159 that is the subject of this objection. Sequence 159 contains 6 paragraphs for a total of a little over one page. The description in patent 526 suggests a potential use to regulate the immune response but does not describe enough to reduce to practice without undue experiments such as which part of the molecule is relevant to practice the invention. To the contrary of the present application, patent 526 description is 1) minimal with a lack of description on the molecule to use and its functional sites for someone to reduce this invention to practice. 2) There is no

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[1]See MPEP 2121.01 and *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968).

[2]See *In re Collins*, 462 F.2d 538, 174 USPQ 333 (CCPA 1972), citing *In re Hoeksema*, see *supra*.

guidance or working evidence presented to support the rejection. 3) the claims are not directed to an EST sequence and related molecules as in U.S. '526 but a function of the SEQ NO:2 molecule to modulate the immune response to treat autoimmune diseases and septic shock, which is not at all described nor reasonably ascertainable from the teachings of US '526.

Fundamentally, US '526 lacks any real disclosure that would put into the public's possession the claimed methods. US '526 merely describes an expressed sequence tag (EST) DNA sequence, among many others, including a matching sequence of TREM-1sv. US '526 does not indicate which one or which combination of the sequence SEQ ID NO 478 being presented in seven different epitopes, must be used to produce a polypeptide usable as a protein therapeutic to modulate an immune response and whether it is an up-modulation or a down-modulation. Consequently, how can one anticipate a complete therapeutic method from such a lack of information unless it refers to the present invention? The present invention fulfills the need by clearly defining the use of TREM-1sv as a protein therapeutic for down-regulating the immune response.

As the US '526 disclosure does not set forth a treatment regimen with the intended purpose of achieving the claimed effect, explicitly or inherently, the claims cannot be anticipated by the US '010 patent. See *Jansen, Id.* and *Perricone, Id.*.

In view of the above, there can be no question that the Office's rejection based on US '526 is not sustainable and should be reversed.

C. The limitations of Claims 1, 3, 5, 11, 15, 16, 40 -42 do not constitute new matter

The examiner asserts that the new claims represent a departure from the application as originally filed by missing clear support for " a composition comprising at least a portion of amino acid 1 to 136..." (Official Action of October 21, 2005 at pages 9-10). This position is simply reiterated in the Advisory Action of August 24, 2006.

Support for the phrase in claims 1 and 3 of " any soluble polypeptide having at least a portion of amino acid 36 to 114 of SEQ ID NO:2, the whole portion ... or more than the whole portion..." is presented in great detail in the specification paragraphs 55, 59, 60, 72, 73, 75, 76, 78, 80 in which "...present invention also includes, but is not limited to variants or biological function equivalents of the TREM-1 splice variant..." "...variants and further variants with deletion and or addition in any combination..." are presented and thus referred to in the claims as being "...any soluble polypeptide having at least a portion of amino acid 36 to 114 of SEQ ID NO:2, the whole portion ... or more than the whole portion...".

Claim 42 is supported at paragraph [0031]

Appellants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the above remarks, Appellants request that all of the rejections be REVERSED.

Respectfully submitted,

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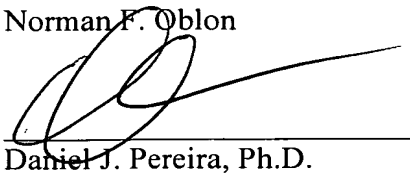

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APPENDIX 1 (CLAIMS)

1. (Previously Presented) A method of modulating an immune response comprising administering to an animal, in need thereof, a composition of soluble polypeptides with at least a portion of amino acids 1 to 136 of SEQ ID NO:2 or a polypeptide mimetic thereof, in an amount effective to modulate the levels of TREM-1 and /or TREM-1SV ligand binding activity whereby the immune response is modulated in the animal.

2. (Canceled)

3. (Previously Presented) The method of claim 1, wherein said polypeptide has at least a portion of amino acids 36 to 114 of SEQ.ID.NO:2, the whole portion of amino acids 36-114 of SEQ ID NO:2, or more than the whole portion of amino acids 36-114 of SEQ ID NO:2.

4. (Canceled)

5. (Previously Presented) The method of claim 1 or 3, wherein said immune response is an inflammatory response.

Claims 6-10. (Canceled)

11. (Previously Presented) The method of claim 1 or 3, wherein said polypeptide is admixed with a pharmaceutical carrier.

Claims 12-14 (Cancelled)

15. (Previously Presented) The method of claim 1 or 3, wherein the animal is suffering from a disease or condition is selected from the group consisting of organ transplant/rejection, bone marrow transplant/rejection, graft versus host disease, infectious disease, and an autoimmune disease.

16. (Previously Presented) The method of claim 15, wherein the disease or condition is an infectious disease and which is septic arthritis or septic shock.

17-39. (Canceled)

40. (Previously Presented) The method of claim 15, wherein the disease or condition is an autoimmune disease.

41. (Previously Presented) The method of claim 1, wherein the composition modulates LPS-induced cytokine production.

42. (Previously Presented) The method of claim 1 or 3, wherein the animal is a human.

APPENDIX II (EVIDENCE)

1. Bouchon et al., *Nature* 410:1103, 2001 (made of record on May 27, 2004)
2. Gibot et al., J Exp Med. 200:1419, 2004 (made of record on September 12, 2005).
3. Kelker et al. *J. Mol. Biol.* 342:1237, 2004 (made of record on September 12, 2005)
4. Kelker et al. *J. Mol. Biol.* 344:1175, 2004 (made of record on September 12, 2005)
5. chapter 16 p. 427-29 of Immunology by H. N. Eisen (made of record on June 21, 2006)
6. Chapter 7 pp. 7.1 -7.3 of Immunology by I. M. Roitt et al (made of record on June 21, 2006)
7. Declaration under 37 C.F.R. § 1.132 of Marie-Claude Gingras (made of record on May 27, 2004)

RELATED PROCEEDINGS APPENDIX

None.